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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,782	10/17/2003	Harald W. Sontheimer	2006636-0064	7705

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
10/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/686,782	SONTHEIMER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15-20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-27-08 has been entered.

Applicants' remarks filed 8-27-08 have been entered. Claims 1, 15-20 and 22-24 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 15-20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering chlorotoxin fused to a radioisotope to neuroectodermal tumors in vitro or via intravenous administration or intracavity injection of brain in vivo, does not reasonably provide enablement for delivering various cytotoxic moieties, including protein or nucleic acid, to a neuroectodermal tumor in vivo by administering a composition comprising a chlorotoxin fused to a cytotoxic moiety, including proteins, to an individual via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 1, 15-20 and 22-25 are directed to a method of delivering a cytotoxic moiety to a neuroectodermal tumor comprising administering a composition comprising an agent consisting of chlorotoxin fused to a cytotoxic moiety to an individual having a neuroectodermal tumor, such that the agent specifically binds to the tumor. Claim 15 specifies the cytotoxic moiety is selected from the group as recited in the claims. Claims 16 and 20 specify the tumor is selected from the group as recited in the claims. Claim 17 specifies the chlorotoxin can be native, synthetic, or recombinant chlorotoxin. Claims 18 and 19 specify the neuroectodermal tumor is a glioma.

Claim 22 specifies the composition further comprises a pharmaceutically acceptable carrier. Claims 23 and 24 specify the composition is suitable for parenteral administration, such as intravenous, intramuscular, intrathecal and subcutaneous administration.

The specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma and metastatic melanoma etc. in a tissue sample by using chlorotoxin. The declaration by Dr. Alison O'Neill filed 5-25-07 discloses that TM-601 is a synthetic version of chlorotoxin and intravenous administration of ^{131}I-TM601 resulted in tumor-specific localization of ^{131}I-TM601 in malignant glioma, prostate cancer, non-small cell lung carcinoma, metastatic melanoma and colon cancer (e.g. paragraph 4 and 6). The claims encompass delivering a cytotoxic moiety, such as a protein, to various neuroectodermal tumors, including ependymonas, medulloblastomas, meuroblastomas, gliomas, gangliomas, pheochromocytomas, melanomas, small cell lung carcinoma, Ewing's sarcoma, and metastatic tumors in the brain, in vivo by administering a composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15 via various administration routes. The specification fails to provide adequate guidance and evidence for how to deliver various cytotoxic moieties, including proteins, other than radioisotope to various neuroectodermal tumors in vivo via various administration routes, including intraperitoneal, oral, topical, intravenous, intramuscular, intrathecal and subcutaneous administration etc. The specification and Dr. O'Neill's declaration only disclose in vitro data of how to deliver the cytotoxic moiety to a tissue sample and in vivo delivery of radioisotope to neuroectodermal tumors via chlorotoxin, however, the specification fails to enable the delivery of chlorotoxin-cytotoxic moiety, such as protein, to various neuroectodermal tumors in vivo.

The art of delivering a protein complex to various target sites in vivo was unpredictable at the time of the invention. The administration route includes intraperitoneal, oral, topical, intravenous, intramuscular, intrathecal and subcutaneous administration etc. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. Hamman et al., 2005 (Biodrugs, Vol. 19, No. 3, p. 165-177) points out problems with oral administration of peptide or protein drugs. "The main reasons for the low oral bioavailability of peptide drugs are pre-systemic enzymatic degradation and poor penetration of the intestinal mucosa" (e.g. abstract). Barriers limiting the oral bioavailability of peptide drugs include physical barrier, such as cell membranes and tight junctions between adjacent epithelial cells, mucus layer and efflux system, enzymatic barrier, fast elimination from the systemic circulation, the potential to develop an immune response, uptake by non-target tissues, and inefficient target cell entry (e.g. p. 166, right column). The peptide drugs administered via administration routes other than oral administration also would encounter the physical barriers as discussed and above, the enzymatic barrier, potential to develop immune response, and uptake by non-target tissues. Torchilin et al., 2003 (DDT, Vol. 8, No. 6, p. 259-266) discusses the problems of protein delivery in vivo. "The use of protein and peptide as therapeutic agents is hampered by their rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system (RES) and accumulation in non-targeted organs and tissues" (e.g. p. 259, right column, last paragraph). There is no evidence of record that demonstrates delivery of various cytotoxic moieties, including proteins, other than radioisotope to various neuroectodermal tumors in vivo by

administering a composition comprising chlorotoxin-cytotoxic moiety via various administration routes. Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how to practice the claimed invention.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, the level of skilled artisan which is high, and the unpredictable nature of the art.

Applicants cite Figures 4, 9 and 12 of the specification, US Patents 5,905,027, which is parent application of instant invention, and argue that example 17 of US Patent 5,905,027 shows injection of ^{131}I-TM-601 into cerebellum of a mouse result in tumor-selective uptake of ^{131}I-TM-601. Example 23 shows treating glioma cells with a chlorotoxin-GST fusion protein attached to saporin results in significant killing of the glioma cells. Applicants further cite declaration by Dr. Alison O'Neill and argue uptake of ^{131}I-labeled chlorotoxin in glioma cells in human patient (amendment, p. 4-6). This is not found persuasive because of the reasons set forth above. The specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma and metastatic melanoma etc. in a tissue sample (in vitro) by using chlorotoxin. The declaration by Dr. Alison O'Neill filed 5-25-07 discloses that TM-601 is a synthetic version of chlorotoxin and intravenous administration of ^{131}I-TM601 resulted in tumor-specific localization of ^{131}I-TM601 in malignant glioma, prostate cancer, non-small cell lung

carcinoma, metastatic melanoma and colon cancer (e.g. paragraph 4 and 6). The claims encompass delivering a cytotoxic moiety, such as a protein, to various neuroectodermal tumors, including ependymonas, medulloblastomas, meuroblastomas, gliomas, gangliomas, pheochromocytomas, melanomas, small cell lung carcinoma, Ewing's sarcoma, and metastatic tumors in the brain, in vivo by administering a composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15 via various administration routes. The specification fails to provide adequate guidance and evidence for how to deliver various cytotoxic moieties, including proteins, other than radioisotope to various neuroectodermal tumors in vivo via various administration routes. Example 17 shows direct injection into cerebellum and example 23 shows in vitro administration of chlorotoxin. Declaration of Dr. O'Neill shows intracranial and intravenous administration of chlorotoxin. There is no evidence of record that demonstrates delivery of a cytotoxic moiety other than radioisotope to various neuroectodermal tumors in vivo via various administration routes, including intraperitoneal, oral, topical, intramuscular, intrathecal and subcutaneous administration etc. The art of delivering a protein complex to various target sites in vivo was unpredictable at the time of the invention. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.
/Shin-Lin Chen/

Primary Examiner, Art Unit 1632